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Exhibit I

Attorney Docket No. 701039-054682-C1-CPA PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Marsha A. Moses, *et al.*

Application No.: 09/469637

Filed: December 22, 1999
(CPA filed February 20, 2002)

For: *"Non-Invasive Enzyme Screen for Cancer" (as Amended)*

Group Art Unit: 1651

Examiner: Gitomer, Ralph J.

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

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_____ By: _____
Date of Signature and of Mail Deposit Attorney for Applicants

DECLARATION OF MARSHA MOSES UNDER 37 C.F.R §1.132

Dear Sir:

I, Marsha Moses, hereby declare that:

1. I received my Ph.D. from Boston University in biochemistry. I am currently an Associate Professor, Department of Surgery, Harvard Medical School, and a Research Associate in the Department of Surgical Research, Children's Hospital Medical Center, Boston, MA. A copy of my "biographical sketch" is attached hereto as Exhibit I (A).

I, Marsha Moses, further declare that:

2. I have been informed and understand that certain claims have been rejected under 36 U.S.C. §102(b) as being anticipated by Ueda (Nippon Hinyokika Gakkai Zasshi entitled "A Study on Cathepsin B Like Substance in Patients with Urological Cancer"); Guolan (Huaxi Yike Caxue Xuebao entitled "The Value of Urine Cysteine Proteinase and Serum CA125 Measurement in Monitoring the Treatment of Malignant Ovarian Tumor"); Okubo (JP-4-1 10660 entitled "Reagent for Liver Disease Diagnosis") and Brunner (Patent No. 6,224,865 entitled "Suppression of Inhibitors,"). It is my understanding that the Examiner asserts that certain pending claims are anticipated by prior art that pertains to cysteine proteinases (Ueda and Guolan), calpains (Okubo), and increased concentrations of matrix degrading enzymes (Brunner).

3. Accordingly, the purpose of this Declaration is to provide my opinion as to what these references would have taught or suggested to one of ordinary skill in the art at the time the claimed invention was made.

4. By way of background, it is well-recognized that proteolytic enzymes play an important role in physiologic and pathologic processes The four distinguishable categories of proteolytic enzymes (cysteine-, serine-, aspartic-, and metalloproteases) are named, and classified according to their essential catalytic component, e.g., an amino acid, in their active site. In short, serine and cysteine proteases utilize their HO- and HS-side chains, aspartate proteases utilize aspartate residues, and metalloproteases utilize heavy metals, to immobilize and polarize a water molecule so that the oxygen atom in water becomes a nucleophile, which attacks the carbonyl-carbon of an amide bond to be cleaved in the type I collagen molecule The following subsections A-D summarize the four classes of proteases and general properties of each group.

A. Asparate Protcases

Aspartic proteases have a catalytic aspartate residue at their active site More than 8 families (denoted Al-A9) have been identified, three of which (pepsin, retropepsm and cauliflower mosaic virus) have been grouped into a single clan (AA), as they are thought to share a common ancestry.

B. Cysteine Proteases

Cysteine proteases are proteases of the subclass EC3.4.22 that have a cysteine residue in the active site that can be irreversibly inhibited by sulphydryl reagents. Cysterne proteases include cathepsins, pepsinand calpains. For example, Cathepsins B, L and S are lysosomal enzymes with acidic pH optima, and degrade intracellularly phagocytosed matrix molecules. They can also act as extracellular proteinases at near to neutral pH. The cathepsins are inhibited by protease inhibitors called cystatins.

Cathepsin B has two forms, the lysosomal active form, which is unstable at neutral pH, and a higher molecular weight form, which remains stable at neutral pH and is secreted extracellularly from stimulated connective tissue cells and activated macrophages. Cathepsin B is found in osteoblasts.

C. Serine Proteases

Serine proteases belong to a group of endoproteases from both animal and bacterial sources that share a common reaction mechanism based on formation of an acyl-enzyme intermediate on a specific active serine residue. Serine proteases are all irreversibly inactivated by a series of organophosphorous esters, such as di-iso-propylfluorophosphate (DFP), and by naturally-occurring inhibitors, such as serpins. Examples of serine proteases include trypsin, chymotrypsin, and the bacterial enzyme subtilisin.

D. Metalloproteases

Metalloproteases are the most diverse of the four main types of protease, with more than 30 families identified to date. In these enzymes, a divalent cation, usually zinc, activates the water molecule. The metal ion is held in place by amino acid ligands, usually three in number. The known metal ligands are His, Glu, Asp or Lys and at least one other residue is required for catalysis, which may play an electrophillic role. There are many types of metalloproteases, one of which is the matrix metalloproternase.

5. Matrix metalloproteinases (MMPs), proteolytic enzymes that degrade extracellular matrix, are members of a subfamily of proteinases, which includes collagenases (MMP-1, -8, -13 and -18), stromelysins (MMP-3, -10, -11, -7 and -12), gelatinases (MMP-2 and -

9) and membrane type MMPs (MT-MMPs) (MMP-14, -15, -16, -17). These enzymes, which require a divalent cation for activity, are normally expressed early in the development of the embryo, for example, during hatching of an zygote from the zona pellucida, and again during the process of attachment of the developing embryo to the inside of the uterine wall.

6. Accordingly, there are four major proteolytic enzyme classes which are distinguishable based on structure, function, and their essential catalytic component. The Examiner alleges that Ueda and Guolan anticipate the claimed invention. However, the Ueda and Guolan references cited by the Examiner do not teach detection of matrix metalloproteinases, as claimed by the instant invention. Rather, Ueda and Guolan teach detection of cysteine proteinases, an entirely different class of protease enzymes that are distinguishable in structure and function from matrix metalloproteinases. Therefore, it is my belief that Ueda and Guolan do not anticipate the claimed invention.

7. Similarly, calpains are structurally related intracellular multidomain cysteine proteases containing a papain-related catalytic domain, whose activity depends on calcium. Calpains are calcium-activated cytoplasmic proteases containing the EF-hand motif. Calpain I is activated by micromolar calcium, calpain II by millimolar calcium. Calpain has two subunits, the larger (80 kB) has four domains one homologous with papain, one with calmodulin, while the smaller (30 kD) has one domain that is homologous with calmodulin. Calpains are believed to participate in intracellular signaling pathways mediated by calcium ions.

8. The Examiner alleges that Okubo anticipates the claimed invention for teaching the use of an antibody to the kininogen-calpain complex for the diagnosis of hepatic disease. While calpains are members of the protease family, calpains are not metalloproteases, and certainly not *matrix* metalloproteinases. In short, it is my belief that Okubo does not anticipate the claimed invention because Okubo does not teach detection of matrix metalloproteinases, as claimed by the instant invention.

9. Matrix metalloproteinases are proteolytic enzymes that degrade extracellular matrix. Brunner discloses that increased concentrations of the inhibitor of the protease or the non-proteolytic matrix-degrading enzyme has been established to be a prognostic factor

indicating a poor prognosis for the patient having the type of malignant tumor in question. While Brunner teaches detection of inhibitors of proteases, the claimed invention is direct to detection and correlation of the presence or absence of a matrix metalloproteinase in a sample, thereby facilitating the diagnosis of cancer. Thus, it is my belief that Brunner does not anticipate the claimed invention.

10. In conclusion, based on at least the foregoing, it is my opinion that the pending claims are novel in light of Udea, Guolan, Okubo and Brunner.

11. I hereby declare that all statements made herein of my own knowledge as true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Marsha O. Moses Ph.D. 1-12-04

MARSHA MOSES, PHD. DATED